

5 WHAT IS CLAIMED IS:

- 10 1. A controlled-release dosage form comprising an opioid agonist; an opioid antagonist; and a controlled release material; said dosage form releasing during a dosing interval an analgesic or sub-analgesic amount of the opioid agonist along with an amount of said opioid antagonist effective to attenuate a side effect of said opioid agonist selected from the group consisting of anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, tolerance, and a combination of any of the foregoing, said dosage form providing analgesia for at least about 8 hours when administered to human patients.
- 15 2. The controlled release dosage form of claim 1, wherein the dose of antagonist released during the dosing interval enhances the analgesic potency of the opioid agonist.
- 20 3. The controlled-release dosage form of claim 1, wherein the opioid agonist and the opioid antagonist are released at substantially proportionate rates.
- 25 4. The controlled-release dosage form of claim 1, wherein the dosage form is administered via a route selected from the group consisting of orally for gastrointestinal absorption, transdermally, via oral mucosa, intranasally, via injection, and rectally.
- 30 5. The controlled-release dosage form of claim 1, wherein the dosage form comprises a solid, oral dosage form.
- 35 6. The controlled-release dosage form of claim 1, wherein the dosage form comprises a transdermal delivery system.
7. The controlled-release dosage form of claim 1, wherein the dosage form comprises an injectable formulation

- 5 8. The controlled-release dosage form of claim 1, wherein the dosage form comprises an intranasal formulation.
9. The controlled-release dosage form of claim 5; wherein the opioid agonist and the antagonist are contained in a plurality of substrates coated with a coating
10 comprising said controlled-release material, said substrates being selected from the group consisting of granules, pellets, beads and spheroids.
10. The controlled-release oral dosage form of claim 1, wherein the opioid antagonist is treated to modify its release rate before it is combined with the opioid agonist, such that when the opioid agonist and the treated antagonist are combined into the controlled-release dosage form, the opioid agonist and antagonist are released from the dosage form at substantially proportionate rates.
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11. The controlled-release dosage form of claim 1, wherein the dosage form is orally administered and said opioid antagonist is treated to modify its release rate before it is combined with the opioid agonist, such that when the opioid agonist and the treated antagonist are combined into the controlled-release dosage form, the dosage form releases the agonist and the antagonist at such rate that the opioid agonist and the opioid antagonist are therapeutically effective over the dosing interval.
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12. The controlled-release dosage form of claim 1, wherein the opioid antagonist is present as granulates comprising the opioid antagonist dispersed in a first controlled release matrix, and wherein the opioid agonist is present as granulates comprising the opioid agonist dispersed in a second controlled-release matrix, the first controlled-release matrix providing controlled-release of the opioid antagonist and the second matrix providing controlled-release of the opioid agonist.
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13. The controlled-release oral dosage form of claim 12, wherein the oral dosage form releases the opioid agonist and the antagonist at substantially proportionate rates.
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- 5 14. The controlled-release oral dosage form of claim 5, wherein the opioid antagonist is prepared as granulates comprising the antagonist dispersed in a controlled-release matrix, said granulates being combined with the opioid agonist and a further controlled release material, such that the opioid antagonist and opioid agonist are preferably released at substantially the same proportionate rate.
- 10 15. The controlled-release dosage form of claim 1, wherein the opioid antagonist is selected from the group consisting of naloxone, naltrexone, diprenorphine, etorphine, dihydroetorphine, pharmaceutically acceptable salts thereof and mixtures thereof.
- 15 16. The controlled-release dosage form of claim 1, wherein the opioid agonist is selected from the group consisting of oxycodone, morphine, hydromorphone, hydrocodone and pharmaceutically acceptable salts thereof.
- 20 17. The controlled release dosage form of claim 15, wherein said opioid agonist is a bimodally-acting opioid agonist selected from the group consisting of morphine, codeine, fentanyl analogs, pentazocine, methadone, buprenorphine, enkephalins, dynorphins, endorphins and similarly acting opioid alkaloids and opioid peptides.
- 25 18. The controlled-release dosage form of claim 1, wherein the amount of the opioid receptor antagonist administered is about 100 to about 1000 fold less than the amount of the opioid agonist administered.
- 30 19. The controlled-release dosage form of claim 1, wherein the dosage form provides controlled-release of the opioid agonist and opioid antagonist over about a 12 hour period.
- 35 20. The controlled-release dosage form of claim 1, wherein the dosage form provides controlled-release of the opioid agonist and opioid antagonist over about a 24 hour period.

- 5 21. A controlled-release dosage form comprising an opioid agonist; an opioid antagonist and a controlled release material; said dosage form releasing during a dosing interval an analgesic or sub-analgesic amount of the opioid agonist along with an amount of said opioid antagonist effective to enhance the potency of said amount of opioid agonist released from the dosage form, said dosage form providing analgesia for at least about 8 hours when administered to human patients.
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22. The controlled-release dosage form of claim 21, wherein the amount of the opioid receptor antagonist administered is about 100 to about 1000 fold less than the amount of the opioid agonist administered.
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23. The controlled release dosage form of claim 21, wherein said amount of opioid antagonist is simultaneously effective to attenuate a side effect of said opioid agonist selected from the group consisting of anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, tolerance, and a combination of any of the foregoing.
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24. The controlled-release dosage form of claim 21, wherein the opioid antagonist is selected from the group consisting of naloxone, naltrexone, diprenorphine, etorphine, dihydroetorphine, pharmaceutically acceptable salts thereof and mixtures thereof.
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25. The controlled release dosage form of claim 24, wherein said opioid agonist is a bimodally-acting opioid agonist selected from the group consisting of morphine, codeine, fentanyl analogs, pentazocine, methadone, buprenorphine, enkephalins, dynorphins, endorphins and similarly acting opioid alkaloids and opioid peptides.
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26. A method for enhancing the analgesic potency of an opioid analgesic contained in a controlled release dosage form, comprising preparing a controlled release dosage form containing an opioid agonist; an opioid antagonist; and a controlled release material in a manner such that said dosage form delivers to human patients during an intended dosing interval an analgesic or sub-analgesic amount of the opioid
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agonist along with an amount of said opioid antagonist effective to enhance the potency of said amount of opioid agonist released from the dosage form, said dosage form providing analgesia for at least about 8 hours when administered to human patients.

27. The method of claim 26, wherein the amount of the opioid receptor antagonist administered is about 100 to about 1000 fold less than the amount of the opioid agonist administered.

28. The method of claim 27, wherein said amount of opioid antagonist is simultaneously effective to attenuate a side effect of said opioid agonist selected from the group consisting of anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, tolerance, and a combination of any of the foregoing.

29. The method of claim 28, wherein the opioid antagonist is selected from the group consisting of naloxone, naltrexone, diprenorphine, etorphine, dihydroetorphine, pharmaceutically acceptable salts thereof and mixtures thereof.

30. The method of claim 29, wherein said opioid agonist is a bimodally-acting opioid agonist selected from the group consisting of morphine, codeine, fentanyl analogs, pentazocine, methadone, buprenorphine, enkephalins, dynorphins, endorphins and similarly acting opioid alkaloids and opioid peptides.

31. The method of claim 30, wherein the opioid agonist and the opioid antagonist are delivered from the dosage form at substantially the same proportionate rate.

32. The method of claim 26, further comprising: (i) pretreating either the opioid agonist or the opioid antagonist to modify its release rate; and (ii) combining the pretreated drug with the other drug to produce the dosage form in which the opioid agonist and the opioid antagonist are delivered from the dosage form at substantially the same proportionate rate.

- 5 33. A method for attenuating a side effect of of an opioid analgesic contained in a controlled release dosage form, said side effect selected from the group consisting of anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, tolerance, and a combination of any of the foregoing, comprising preparing a controlled release dosage form containing an opioid agonist; an opioid antagonist; and a controlled release material in a manner such that said dosage form delivers to human patients during the intended dosing interval an analgesic or sub-analgesic amount of the opioid agonist along with an amount of said opioid antagonist effective to enhance the potency of said amount of opioid agonist released from the dosage form, said dosage form providing analgesia for at least about 8 hours when administered to human patients.
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- 20 34. The method of claim 33, wherein the amount of the opioid receptor antagonist administered is about 100 to about 1000 fold less than the amount of the opioid agonist administered.
- 25 35. The method of claim 34, wherein the opioid antagonist is selected from the group consisting of naloxone, naltrexone, diprenorphine, etorphine, dihydroetorphine, pharmaceutically acceptable salts thereof and mixtures thereof.
- 30 36. The method of claim 35, wherein said opioid agonist is a bimodally-acting opioid agonist selected from the group consisting of morphine, codeine, fentanyl analogs, pentazocine, methadone, buprenorphine, enkephalins, dynorphins, endorphins and similarly acting opioid alkaloids and opioid peptides.
- 35 37. A transdermal delivery system for an opioid analgesic, comprising an opioid agonist and an opioid antagonist contained in a reservoir or matrix and capable of delivery from the device in a controlled manner, such that when the device is applied to the skin of a human patient, the opioid agonist is delivered at a mean relative release rate effective to provide analgesia to said patient for at least 3 days, and the opioid antagonist is delivered at a mean relative release rate sufficient to reduce side effects associated with the opioid agonist but not sufficient to negate the analgesic effectiveness of the opioid.
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38. The transdermal delivery system of claim 37, wherein the amount of antagonist delivered from the transdermal delivery system is effective to enhance the analgesic potency of the opioid agonist delivered from the device.

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39. The transdermal delivery system of claim 37, wherein the amount of the opioid receptor antagonist delivered from the device is about 100 to about 1000 fold less than the amount of the opioid agonist delivered.

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